REMARKS

Claims 1, 3, 4 and 15-20 presently appear in this case. No claims have been allowed. The official action of March 18, 2009, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for treating or attenuating progression of cell necrosis or a neurodegenerative disorder associated therewith, by administering a therapeutically effective amount of an elastase inhibiting agent capable of entering the cell, thereby inhibiting the one or more elastase enzymes within the cell. The invention is based on the discovery that such intracellular elastase enzymes are activated during necrosis and, thus, the progression of such cell necrosis can be attenuated by inhibiting that intracellular elastase in such cells. The invention is further directed to the discovery that administration of a therapeutically sub-effective amount of elastase inhibitor will direct cell necrosis to cell apoptosis, which can be treated by the co-administration of an anti-apoptotic agent. The combination of the elastase inhibiting agent and the anti-apoptotic agent will have a synergistic protective effect on said cells.

Claims 15-17 have been rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating cell necrosis or a neurodegenerative disorder associated therewith, does not reasonably provide enablement for prevention of cell necrosis or a neurodegenerative disorder associated therewith. The examiner states that the term "prevent" means to stop from occurring and thus requires a higher standard for enablement than does "therapeutic" or "treat." This rejection is respectfully traversed.

In order to obviate this rejection, claim 15 has now been amended to delete the term "preventing" and to specify that the method is for "attenuating progression of cell

necrosis or a neurodegenerative disorder associated therewith." The present specification as a whole supports the concept of attenuating progression. Accordingly, this claim language is not new matter. In view of the fact that claims 15-17 no longer are directed toward prevention, the present rejection is no longer applicable. Reconsideration and withdrawal thereof is respectfully urged.

Claims 1, 4, 15 and 17 have been rejected under 35 U.S.C. 102(b) as being anticipated by Gyorkos. The examiner states that Gyorkos teaches administering an elastase inhibitor to a host in need thereof, such as those in need of treatment for Alzheimer's disease (AD). The examiner notes that Gyorkos specifically teaches inhibiting human neutrophil elastase that is secreted by cells. The examiner considers that if the elastase is secreted by cells it must also be present inside the cells in order to be secreted, thus meeting the claim limitations. The examiner assumes that the inhibitors of Gyorkos are inherently capable of entering cells. This rejection is respectfully traversed.

Gyorkos teaches specific novel compounds which are inhibitors of the serine protease human neutrophil elastase (HNE). At column 3, lines 3-5, Gyorkos says that "the compounds are characterized by their ... high selectively with respect to HNE... ." While Gyorkos states at column 3, beginning at line 30, that the compounds are not limited to use for inhibition of human elastase, it goes on to mention that other related proteinases or chymases, tryptases and propyl endopeptidase. However, at column 4, lines 28-31, Gyorkos states that in order to be directed to another desired proteinase, the alpha-substituent to the ketone and to some extent the substituent on the heterocycle must be altered. However, there is no disclosure of how to alter these substituents and how to make the compounds selective to any other proteinase. Thus, HNE is the only proteinase for the inhibition of which there is enabling support in Gyorkos. In the abstract, and at column 1, in the paragraph beginning at

line 41, Gyorkos states that "HNE-mediated processes are implicated in other conditions such as ... Alzheimer's disease... ." However, there are no examples of how Alzheimer's disease is HNE mediated or how it would be treated by means of the Gyorkos invention. The only other mention of Alzheimer's disease in the specification of Gyorkos is the first paragraph of column 4, which relates to a completely different proteinase. As discussed above, there is no disclosure in Gyorkos of how the compound must be modified in order to make it specific to propyl endopeptidase.

The present claims all require that the elastase inhibitor must be capable of entering the cell and be effective against intracellular elastase enzymes. There is no disclosure in Gyorkos that the inhibitor disclosed therein is capable of entering a cell, and being active against an enzyme within the cell. Not all enzyme inhibitors are capable of passing through a cell membrane. In Gyorkos, there is no necessity to do so as Gyorkos is specifically intending to treat HNE which has been secreted by the cells. The examiner has either ignored the claim limitation requiring that the elastase inhibitor be capable of entering the cell, or the examiner is taking the position that such a capability is inherent. However, with respect to inherency, the examiner's attention is invited to MPEP 2112(IV), which states:

> The fact that a certain result or characteristic <u>may</u> occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. ... . "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'"

The examiner has not established that the particular elastase inhibitor disclosed by Gyorkos will necessarily be capable of entering a cell and being active within the cell. Probabilities and possibilities are insufficient. The examiner has submitted no extrinsic evidence that makes clear that the descriptive matter (in this case, the capability of entering a cell) is necessarily described in the thing described in the reference. For this reason alone, none of the present claims are anticipated by Gyorkos.

Furthermore, it would not be obvious to use the substituted oxadiazole tripeptides of Gyorkos, which are specific for HNE (as discussed above), for the treatment of Alzheimer's disease (AD). As Gyorkos recognizes, HNE resides selectively in neutrophils, and is active only when the neutrophils are activated and the HNE is released. While various poly-morphonuclear leukocytes (PMNs) may be involved in Alzheimer's disease, neutrophils are not among them. The brain is an immuno-privileged organ and neutrophils do not participate in the development of AD, nor in the signaling, cell death or the inflammatory process that takes place in the brain of AD patients by microglial cells and astrocytes. See Heneka and O'Banion, "Inflammatory Processes in Alzheimer's Disease," *J. Neuroimmunol.*, 184:69:91 (2007), a copy of which is submitted herewith. Since neutrophils and HNE are not active in the brain, Gyorkos does not anticipate or make obvious the use of the HNE inhibitor thereof in the treatment of Alzheimer's disease. For all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 15 and 17 have been rejected as being anticipated by Miyano. The examiner states that Miyano teaches a method of administering an elastase inhibitor for the management or alleviation of elastase mediated diseases, such as, arthritis. As to the recitation that the elastase inhibitor be capable of entering cells, the examiner states that Miyano teaches a variety of compositions for various administrations of the inhibitor at

column 10, and that there is reasonable basis, absent evidence to the contrary, that the inhibitors of Miyano are capable of entering cells. The examiner states that this rejection is applicable to claims 15 and 17 as they are directed to prevention, which is readable on the administration to any patient population. This rejection is respectfully traversed.

Claims 15 and 17 have been amended to eliminate reference to prevention. There is no suggestion in Miyano to administer an elastase inhibitor for the purpose of attenuating progression of cell necrosis or a neurodegenerative disorder associated therewith. Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 1, 4, 15 and 17 have been rejected under 35 U.S.C. 102(b) as being anticipated by Miyano as evidenced by Proskuryakov. The examiner states that Miyano teach administering an elastase inhibitor to a host in need thereof for the management or alleviation of elastase mediated diseases, such as arthritis, and specifically rheumatoid arthritis. The examiner states that Proskuryakov teach that inflammatory diseases are associated with cell necrosis and since Miyano teach inflammatory diseases such as rheumatoid arthritis, the patient population of claim 1 is met since the diseases are associated with cell necrosis. The examiner states that Proskuryakov is cited as a universal fact to show that the patient population of Miyano meets the limitation of the instant claims. This rejection is respectfully traversed.

Miyano teaches certain specific compounds that selectively inhibit the proteolytic enzyme elastase from human leukocytes (see column 3, lines 34-37). There is no disclosure in Miyano, however, that such compounds are capable of entering a cell and being active on the elastase therein. Nor is there any disclosure that such intracellular activity is necessary for the utility disclosed by Miyano. The disclosure of how the compound is to be administered at column 10, says nothing about whether or not the compound is capable of

entering cells. As discussed hereinabove with respect to Gyorkos, in order for a feature to be inherent it must be certain. It cannot be based on probabilities or possibilities. The examiner has presented no extrinsic evidence that this is necessarily the case. Proskuryakov is silent in this regard. Accordingly, for this reason alone, the anticipation rejection cannot stand.

Furthermore, Miyano is silent as to whether or not the patients having arthritis are in need of treatment of cell necrosis. Again, inherency requires that the thing necessarily occur, not that it is possible. The examiner cites Proskuryakov as extrinsic evidence that cell necrosis necessarily occurs whenever there is inflammation. However, Proskuryakov teaches nothing of the sort. The examiner's attention is directed to the abstract of Proskuryakov which states:

> In the case of necrosis, cytosolic constituents that spill in to extracellular space through damaged plasma membrane may provoke inflammatory response... . The inflammatory response caused by necrosis, ...\

Thus, Proskuryakov only shows that inflammatory response may be caused by necrosis, not that necrosis is a necessary response to inflammation. There is no suggestion that all inflammation is caused by necrosis, or specifically that rheumatoid arthritis inflammation is caused by necrosis or results in necrosis. Therefore, Proskuryakov even if it were available as a reference because of its date, would not be sufficient extrinsic evidence as to establish that cell necrosis is necessarily present in every case of inflammation, or more specifically in the type of inflammation being treated by Miyano. Accordingly, this is another reason why none of the present claims are anticipated by Miyano. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 1, 4, 15 and 17 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Gyorkos and Stein. The examiner states that Gyorkos teaches everything

in the claim, as discussed above, except for the specific elastase inhibitor III. The examiner states that Stein teaches elastase inhibitors and specifically teaches the elected species of the current invention. The examiner states that one would be motivated to treat the patient population of Gyorkos (those with Alzheimer's) using the peptide of Stein. This rejection is respectfully traversed.

Gyorkos teaches the use of inhibitors which are specific to HNE. The inhibitors of Stein are not specific to HNE and therefore it would not be obvious to substitute them for the HNE specific inhibitors of Gyorkos. Furthermore, for the reasons discussed above, it would not be obvious to use the HNE inhibitors of Gyorkos for the treatment of Alzheimer's disease and therefore there would be no motivation to use any other HNE specific inhibitor for the treatment of Alzheimer's disease. For all these reasons, there would be no motivation to combine the elastase inhibitor of Stein, which is non-HNE specific, for the HNE specific inhibitor which is the point of novelty in Gyorkos. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 1, 3, 4, 15 and 17 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Gyorkos and Rohn. The examiner states that Gyorkos teaches everything claimed, as discussed by the examiner in the previous rejections, except for the further administration of an antiapoptotic agent as recited in claims 3 and 16. However, the examiner states that Gyorkos teaches that the inhibitors are useful in the treatment of Alzheimer's disease and Rohn also provides teachings regarding Alzheimer's disease. The examiner states that Rohn provides evidence that there is an association between neurofibrillary tangles (NFTs) and the activation of apoptotic pathways in Alzheimer's disease. The examiner considers that one of ordinary skill art would have been motivated to administer to those with Alzheimer's both the elastase inhibitor as taught by Gyorkos and the

antiapoptotic agent as taught by Rohn, with the reasonable expectation of combined beneficial effects against Alzheimer's. This rejection is respectfully traversed.

As discussed hereinabove, it would not be obvious to use the HNE specific inhibitor of Gyorkos in the treatment of Alzheimer's disease. Neutrophils are not involved in Alzheimer's disease. Thus, one of ordinary skill in the art would not consider it obvious to inhibit an elastase that is only produced by neutrophils and expect it to have any effect on Alzheimer's disease. Rohn provides none of the deficiencies of Gyorkos in this regard as there is no suggestion in Rohn why one of ordinary skill in the art would want to use an HNE specific inhibitor for the treatment of Alzheimer's disease where HNE is not present.

Furthermore, when the elastase inhibitor is used in combination with an anti-apoptotic agent in accordance with the present invention, synergistic results are achieved. Only sub-therapeutic amounts of the elastase inhibitor need be used. This is certainly not suggested by Gyorkos.

For all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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